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EXAMINER

VIVLEMORE, TRACY ANN

ART UNIT

PAPER NUMBER

1635

DATE MAILED: 09/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/038,984

Applicant(s)

LI ET AL.

Examiner

Tracy Vivlemore

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 July 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-7,9,10,15-32,39,42-48,57 and 61-74 is/are pending in the application.
- 4a) Of the above claim(s) 42-47,57,61 and 64-67 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-7, 9, 10, 15-32, 39, 48, 62, 63 and 68-74 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 7/02,4/03,3/04 & 5/04
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-7, 9, 10, 15-32, 39, 48, 62, 63 and 68-74 in the reply filed on July 9, 2004 is acknowledged. The traversal is on the ground(s) that a single search would serve to encompass not only the elected invention but also the non-elected inventions. This is not found persuasive because a search of non-patent literature for a method of attenuating gene expression would not serve as a thorough search for the other claimed inventions.

The requirement is still deemed proper and is therefore made FINAL.

Status of the application

2. Claims 1-7, 9, 10, 15-32, 39, 42-48, 57, 61, 62-74 are pending. Claims 42-47, 57, 61 and 64-67 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on July 9, 2004.

Specification

3. The amendment filed April 28, 2003 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The paragraph beginning on page 36, line 10 has been amended to change the reference to "murine NIH/3T3 cells" to "rat cells". The amendment is supported by an affidavit by one of the inventors

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filed under 37 CFR 1.132 indicating this is an inadvertent error and the cells used in the experiment were rat ROS cells.

4. This amendment is objected to because 1). the changes in the specification are not commensurate in scope with that of the affidavit. The affidavit states the cells to be rat ROS cells while the specification is amended with the broader limitation of "rat", and 2). there is no factual evidence accompanying the affidavit under 37 CFR 1.132 to support the inventor's assertion that the error was inadvertent.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 9, 10, 15-32, 39, 48, 62, 63 and 68-74 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of attenuating the expression of specific disclosed target genes in zebrafish cells or embryos, attenuating the expression of the specific disclosed target gene in avian neural crest tissue explant culture and attenuating the expression of the specific disclosed target gene in rat [murine NIH/3T3] cell culture, does not reasonably provide enablement for attenuating the expression of any gene, in any *in vivo* or *in vitro* vertebrate cell, or for attenuating the expression of any gene in any explant tissue culture or attenuating the expression of any gene in any cell culture type. Moreover, the specification does not reasonably provide enablement for a method for treating a

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disease or infection in an organism. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors as enumerated *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), are considered when making a determination that a disclosure is not enabling: the breadth of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples and the quantity of experimentation needed to make the invention based on the content of the disclosure.

5. The specification teaches introduction of specific double stranded RNAs (dsRNAs) in zebrafish embryos, avian tissue culture explants, and rat [murine NIH/3T3] cells. The dsRNAs target a particular gene, causing an attenuation or inhibition of gene expression, resulting in a particular phenotype. Thus, the specification is enabling for a method of attenuating the expression of the specific disclosed target genes in zebrafish cells or embryos, attenuating the expression of the specific disclosed target gene in avian neural crest tissue explant culture, and attenuating the expression of the specific disclosed target gene in rat [murine NIH/3T3] cell culture, as the specification clearly sets forth a method of attenuating expression of certain specific genes such that a reproducible phenotype is observed.

6. Claims 1-7, 9, 10, 15-32, 39, 48, 62, 63 and 68-74 are drawn to methods of attenuating expression of a target gene in a vertebrate cell. No specific target genes

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are claimed, thus the claimed method encompasses attenuation of all genes in all vertebrate species, including fish, avians and mammals, including humans. The specification is not enabling for the targeting of *any* particular gene as the specification does not provide sufficient guidance as to which genes should be targeted, how the dsRNA is administered such that an effective amount of the dsRNA is provided to obtain a particular phenotype that is capable of attenuating or inhibiting expression of the gene of interest.

7. The unpredictability of attenuating/inhibiting expression of a target gene in vertebrates by RNA interference (RNAi) is evident in post-filing art. With respect to RNAi in vertebrate embryos, the specification provides a working example of targeting well-characterized genes with dsRNA by microinjection in the embryos of one species of vertebrate. However, while Wargelius et al. (Biochem. Biophys. Res. Commun. 1999, vol. 263, p.156-161) initially reported that RNAi functions specifically in the vertebrate zebrafish, two recent reports indicate that RNAi causes non-specific effects in this system. Oates et al. (Developmental Biology 2000, vol. 224, p. 20-28) report that, with regard to the *spt* gene, which was selected because it acts early in development and is phenotypically and genetically well characterized, "dsRNA injected into early zebrafish embryos causes a nonspecific depletion of several endogenous mRNAs, leading to an easily misinterpreted syndrome of developmental defects. Thus, at present, RNAi appears unsuited to application in the zebrafish embryo for the study of zygotic gene activity during development." (see page 21, first column, second full paragraph). Similarly, Zhao et al. (Developmental Biology, 2001, vol 229, p.215-223) report non-

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specific defects in zebrafish embryos injected with dsRNA sequences targeting the maternal gene *poull-1*, the transgene *GFP* and an intron of the zebrafish gene *terra* (see p 215, abstract and pages 220-222). Zhao et al. indicate that the technique needs to be further developed (see page 216, first column, lines 1-3).

8. While it is recognized that introduction of dsRNA that is targeted to a specific gene may result in attenuation of expression of the targeted gene, the degree of attenuation and the length of time that attenuation is achieved is not predictable. For example, Fire (Trends in Genetics, 1999, vol. 15, p 358-363) teaches that post transcriptional gene silencing (PTGS) acts by decreasing the half-life of RNA. The natural stability of an RNA will have a quantitative influence upon its suitability as a PTGS target: naturally stable RNAs are likely to be more dramatically affected whereas RNAs that are rapidly synthesized and degraded might be less affected. Homeostatic regulation mechanisms might also influence the final outcome of PTGAS in that a decrease in the final product could activate a metabolic compensation mechanism that would partially restore expression level (see, p 360, second column, first paragraph). Fire (Nature 1998, vol 391, p. 806-811) further indicates that introduction of dsRNA can result in a mosaic pattern of interference or resistance to interference may be observed. In addition, Fire teaches that the design of the dsRNA is important because not all dsRNA sequences work well. For example, dsRNA segments corresponding to various intron and promoter sequences do not produce detectable interference (see p 809, second column). Fire also cautions that several limitations should be taken into account when designing RNA-interference-based experiments such as (1) a sequence shared

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between several closely related genes may interfere with several members of a gene family and (2) it is likely that a low level of expression will resist RNA-mediated interference for some or all genes and a small number of cells will likewise escape the effect of the interference (see page 810, first column, first full paragraph).

9. The post filing art of Caplen et al. (Gene 2000, vol. 252, p.95-105) provides additional evidence of the unpredictability of dsRNA attenuation/inhibition of a targeted gene in vertebrate cells *in vitro*. Caplen et al. report that although dsRNA inhibits gene expression in cultured *Drosophila* cells, screening of three commonly used cell lines from three different species: human, hamster, and mouse, using cells expressing transgenes both transiently and permanently, produced mixed results. Transient transfection of dsRNA targeted to the β gal transgene into 293 and BHK31 cells resulted either in no effect (293 cells) or a non-specific decrease in gene expression (BHK21 cells). Transfection of dsRNA into mouse NIH/3T3 cells transduced with a retrovirus expressing β gal induced no detectable decrease in gene expression (see pages 102-103).

10. Wianny et al. (Nature Cell Biology 2000, vol.2 p.70-75) have reported that dsRNA can be used as a specific inhibitor of gene activity (targeted against *c-mos* in the oocyte and against *E-cadherin* or a *GFP* transgene in the early mouse embryo) in the mouse oocyte and preimplantation embryo without causing a general translation arrest. However, the authors indicate that it is possible that the early mouse embryo is incapable of an interferon response, resulting in general translation arrest and that there may still be difficulties in using RNAi at later stages (see page 73, under Discussion).

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Thus, the post-filing art clearly suggests that administering dsRNA to vertebrate systems, either *in vitro* or *in vivo*, to attenuate/inhibit target genes is not a reproducible or predictable art.

11. The post-filing art of Zhang et al. (Current Pharmaceutical Biotechnology 2004, vol. 5, p.1-7) reviews the state of the art with regard to RNAi and has this to say about use in mammalian cells. "Use of siRNA in mammalian cells could be just as far-reaching, with the applications extending to functional genomics and therapeutics. But various technical issues must be addressed, especially for large-scale applications. For instance, dsRNA can be delivered to *C. elegans* by feeding or soaking, but effective delivery of siRNAs to mammalian cells will not be so simple."

12. At the time the instant application was filed, and even to date, nucleic acid based therapies were highly unpredictable. The field of RNA interference was in its infancy and gene specific dsRNA inhibition in mammalian cells was also highly unpredictable, even in cells in culture and the ability to inhibit gene expression was variable and unpredictable among different cells lines and different target genes. In particular, in mammalian cells, longer dsRNA molecules were observed to cause the induction of the PKR response, resulting in cell apoptosis and non-specific mRNA expression inhibition. Examples in the literature demonstrate that in some organisms, including zebrafish and mice, the inhibition by double stranded RNA was unpredictable or transient (see for example Oates et al. or Wianny et al). Attempts to 'knock out' gene function in an organism using double stranded RNA administered at the embryonic stage have

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demonstrated that inhibition by double stranded RNA is transient, and function is regained after multiple cell divisions (see for example Wianny et al.).

13. Further, mammals, including humans, have demonstrated an immune response triggered by even small amounts of double stranded RNA that would preclude the use of dsRNA *in vivo* (whole organism) and in *Xenopus* an endogenous dsRAD activity would predict that dsRNA methods would not be effective (see for example Wianny et al. page 74). After the filing date of this Application, the field of RNA interference determined that shorter dsRNA molecules could overcome this PKR response, and resulted in a more predictable inhibitory response, however, guidance for the use of shorter dsRNAs, as discussed in the literature as necessary to more predictably apply the claimed methods, was not provided in the instant specification. Even with the advances made by the field of RNA interference, however, to induce inhibition by RNA interference in mammalian cells in culture, RNA interference is still recognized in the art as not enabled for therapeutic purposes. (See for example, Caplen (RNAi as a gene therapy approach. Expert Opin. Biol. Ther. 2003, Vol. 3, p575-586), Coburn et al. (siRNAs: a new wave of RNA-based therapeutics. Journal of Antimicrobial Chemotherapy. 2003, vol. 51, p753-756) and Agami et al. (RNAi and related mechanisms and their potential use for therapy. Current Opinion in Chemical Biology, 2002, Vol. 6, pages 829-834) for a review on the progression of RNA interference in mammalian cells and the state of the art of RNA interference for therapeutic purposes.)

14. Claims 24 and 25 state that the method of attenuating gene expression can be performed using a broad range of delivery methods, including particle bombardment,

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soaking the cell or organism in a solution of the dsRNAs, electroporation of cell membranes, liposome-mediated delivery, transfection-mediated delivery, injection or perfusion into a body cavity or interstitial space of an organism, systemic administration, or providing the dsRNA with food. It is noted that while prior art references teach administration of dsRNA to invertebrates using several of the broadly disclosed methods (such as microinjection into a body cavity of *C. elegans* and feeding *E. coli* which express dsRNAs to *C. elegans*), the prior art does not address administering dsRNA to vertebrates and thus does not teach successful delivery and attenuation/inhibition of a target gene *in vivo* or *in vitro* in vertebrates.

15. Claim 63 is drawn to a method of attenuating expression of a target gene with a double stranded RNA that is at least 25 nucleotides long. Claims 72 and 73 depend from claim 63 and claim that the target gene is associated with a disease or pathogen. Thus, claims 72 and 73, in combination with claim 63, encompass methods of treating a disease in an organism. With regard to a method of treating a disease or infection, the specification does not provide sufficient guidance for selecting the target gene, nor does the specification disclose the appropriate route of administration or amount of the dsRNA required such that a sufficient amount of dsRNA would be taken up by the appropriate tissues and effectively attenuate gene expression. Moreover, the specification does not provide guidance as to which diseases or infections are suitable for treatment, nor does the specification provide any working examples of treating disease or infection in a mammal.

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16. Caplen (2003) points out that, even post filing in 2003, "Many of the problems associated with developing RNAi as an effective therapeutic are the same as encountered with previous gene therapy approaches. The key issues of delivering nucleic acids to the required tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system..." (see page 581) Coburn et al. also points out that the major impediment to using RNA interference as a therapeutic is that gene expression is transient and the delivery methods used for RNAi are not effective for therapeutic purposes (see for example p 754, first column, last paragraph). Those of skill in the art of RNA interference are optimistic about the potential of RNA interference as a therapeutic tool, but even with the advances made subsequent to the filing of the instant application, the field recognizes that therapeutic methods are not yet effective.

17. RNA interference methods for therapeutic methods encounter the same problems long recognized in other nucleic acid based therapies, particularly with regard to the inability to specifically deliver an effective concentration of a nucleic acid to a target cell, such that a target gene is inhibited to a degree necessary to result in a therapeutic effect. The problems of nucleic acid based therapies are well known in the art. For example, at the time the instant invention was made, the therapeutic use of nucleic acids was a highly unpredictable art due to obstacles that continue to hinder the therapeutic application of nucleic acids *in vivo* (whole organism) (see for example Agrawal et al. (Molecular Medicine Today, 2000, vol 6, p 72-81), Branch (TIBS 1998, vol. 23, p. 5-50), Green et al. (J. Am Coll. Surg., 2000, vol 191, p 93-105), Jen et al.

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(Stem Cells 2000, Vol. 18, p 307-319)). Such obstacles include, for example, problems with delivery, target accessibility and the potential for unpredictable nonspecific effects. These references discuss the problems of nucleic acid based therapies in reference to antisense and gene therapy methods, however, as pointed out in Caplen (2003), RNA interference encounters similar problems as other nucleic acid based therapies.

18. Jen et al. state (see page 313, second column, second paragraph) "One of the major limitations for the therapeutic use of AS-ODNS and ribozymes is the problem of delivery... presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes (see p 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive."

19. Green et al. state, "It is clear that the evolution of antisense technology from a laboratory research tool into a mechanism for designing active and effective drugs is far from complete. Although there is little doubt that systemically administered antisense ODNS can inhibit the expression of specific genes in patients, the effectiveness of such therapy in modifying the course of a particular illness has not yet been established....clearly, additional work must be done to unravel the complex problems associated with drug delivery, mRNA targeting and aptameric, nonantisense effects."

20. Wang et al. (Antisense and Nucleic Acid Drug Delivery, 2003, vol. 13, p.169-189) describe the difficulties in delivering of antisense oligonucleotides, "Antisense ODNs, delivered parenterally or nonparenterally, must be sufficiently absorbed from the site of

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administration, distributed to various tissues, taken into target cells, and possess sufficient residence time and concentration at the sites of action to elicit effective biologic responses. For this to occur, it is necessary that the ODN drug be resistant to chemical or enzymatic degradation throughout the entire delivery process. Native ODNs, with a natural phosphodiester backbone, are rapidly degraded by abundant nucleases present *in vivo*.”

21. Crooke, (Antisense Research and Application, Chapter 1, Springer-verlag, New York. 1998) states on p. 3, paragraph 2, “extrapolations from *in vitro* uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate and, in fact, there are now several lines of evidence in animals and man [that] demonstrate that, even after careful consideration of all *in vitro* uptake data, one cannot predict *in vivo* pharmacokinetics of the compounds based on *in vitro* studies [references omitted].”

22. Flanagan et al., (Nature Biotechnology. Vol. 17 p. 48-52 January 1999) states on p. 48, paragraphs 1-3 and p. 51, paragraphs 2 and 6, that antisense therapies also face major problems in delivering amounts of oligonucleotides to the *in vivo*, intracellular target that are sufficient to inhibit gene expression.

23. Post-filing art describes the ongoing difficulties in using RNAi to treat disease. Check (Nature, 2003, vol. 425, p. 10-12) reports “...[S]cientists must figure out how to make RNAi therapies work. They are facing some formidable technical barriers, chief among which is the problem of getting siRNAs into the right cells. This is not a trivial issue, because RNA is rapidly broken down in the bloodstream and our cells don’t readily absorb it through their membranes. And even when RNA gets into its target cell,

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scavenger proteins quickly chew it up.” (see page 11, middle column, second full paragraph). Check describes that delivery methods are of concern to many researchers. In column 2 of page 11: “ ...‘The major hurdle right now is delivery, delivery, delivery’ says Sharp” and in column 3 of the same page, “Khvorova believes that the medical benefits of RNAi will be huge if the delivery issues can be resolved. ‘But we’ve looked at a lot of the delivery methods that have been used for antisense, and so far I haven’t been impressed,’ she says.”

24. Opalinska et al. (Nature Review, 2002, vol 1, p. 503-514) state “[I]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA” and in column 2 of the same page, “Another problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded.”

25. Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods *in vivo* in all vertebrates, with a resultant therapeutic

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outcome, as claimed. The specification provides examples wherein long dsRNA is delivered to avian neural crest tissue and rat [murine NIH/3T3] cells *in vitro*, however, cell culture examples are generally not predictive of *in vivo* inhibition and the methods of delivery of the exemplified cell line would not be applicable to delivery of dsRNA to a mammal. Often formulations and techniques for delivery *in vitro* (cell culture) are not applicable *in vivo* (whole organism) (see for example Jen et al., page 313, second column, second paragraph). For example, Agrawal et al. (see p 79-80, section entitled "Cellular uptake facilitators for *in vitro* studies") states "The cellular uptake of negatively charged oligonucleotides is one of the important factors in determining the efficacy of antisense oligonucleotides... ..*In vitro*, cellular uptake of antisense oligonucleotides depends on many factors, including cell type, kinetics of uptake, tissue culture conditions, and chemical nature, length and sequence of the oligonucleotide. Any one of these factors can influence the biological activity of an antisense oligonucleotide." Agrawal discusses these factors in relation to antisense, but they would also apply to dsRNA. Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results.

26. Given these teachings, the skilled artisan would not know *a priori* whether introduction of dsRNA into vertebrate cells, either *in vivo* or *in vitro*, by the broadly disclosed methodologies of the instant invention, would result in successful attenuation/inhibition of a target gene. One of skill in the art would not know how to

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deliver dsRNA to an organism in such a way that would ensure an amount sufficient to attenuate expression of a target gene is delivered to the proper cell.

27. In fact, the state of the art is such that successful delivery of polynucleotide sequences to a target cell *in vivo* or oligonucleotides sequence *in vivo* or *in vitro*, such that the polynucleotide or oligonucleotide provides the requisite biological effect to the target cells/tissues/organs, must be determined empirically. Methods of inhibiting gene expression using nucleic acids *in vivo* are unpredictable with respect to delivery of the nucleic acid molecule such that the nucleic acid molecule is targeted to the appropriate cell/organ, at a bioeffective concentration and for a period of time such that the nucleic acid molecule is effective in, as in the instant application, attenuating or inhibiting expression of a target gene such that the organism exhibits a loss of function phenotype.

28. The specification does not provide the guidance required to overcome the art-recognized unpredictability of dsRNA for use in RNA interference in all vertebrate cells and in the therapeutic application of RNAi in any vertebrates, including mammals and humans. The field of RNA interference does not provide that guidance, such that the skilled artisan would be able to practice the claimed therapeutic methods.

29. Thus, while the specification is enabling for the examples set forth in the specification, the specification is not enabling for the broad claims of introducing any dsRNA for *any* target gene in *any* cell or animal as the art of attenuating gene expression by introducing dsRNA into a cell or organism is neither routine nor predictable. Thus, one of skill in the art could not practice the invention commensurate

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in scope with the claims without undue, trial and error experimentation and therefore, claims 1-7, 9, 10, 15-32, 39, 48, 62, 63 and 68-74 are not enabled.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 9, 10, 15-32, 39, 48, 62, 63 and 68-74 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

30. Claims 1-7, 9, 10, 15-32, 39, 48, 62, 63 and 68-74 are drawn to methods of attenuation of gene expression in vertebrate cells. As described in the previous enablement rejection, the claims encompass the attenuation of any gene in any vertebrate cell and the treatment of any disease state in any vertebrate organism. The specification provides insufficient written description to support the genus encompassed by the claims.

31. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The

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specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

32. MPEP 2163 states in part, "An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004) (The patent at issue claimed a method of selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product, however the patent did not disclose any compounds that can be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which peptides, polynucleotides, and small organic molecules selectively inhibit PGHS-2. The court held that "[w]ithout such disclosure, the claimed methods cannot be said to have been described.")"

33. With the exception of the target genes and cells as enumerated in the previous 112 rejection, the skilled artisan cannot envision the detailed structure of the encompassed genes and vertebrate cells, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481,

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1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

34. Therefore, only the disclosed target genes and cells, but not the full breadth of the claim (or none of the many genes, cells, diseases or organisms encompassed by the claim) meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-10, 15-26, 28-30, 62, 63, and 68- 74 are rejected under 35 U.S.C. 102(e) as being anticipated by Fire et al. (US 6,506,559, January 14, 2003).

35. Claims 1-10, 15-26, 28-30, 62, 63, and 68- 74 are drawn to methods of attenuating gene expression in a vertebrate cell as described in the previous 112 rejections.

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36. Fire et al. disclose a method of inhibiting gene expression *in vitro* by supplying a cell with a dsRNA. The disclosure and claims of Fire et al. are drawn to animal cells, including vertebrates (see column 8, lines 35-51), the genes targeted can be endogenous or a transgene, which is a foreign gene, or can be from a pathogen (see column 6, lines 45-49). Fire et al. discloses the limitation on hybridization conditions in column 7, line 67-column 8 line 4 and the dsRNAs used in the disclosed examples were purified without phenol and chloroform. The dsRNA can be formed from 1 or 2 strands (see column 4, lines 41-46). The method of Fire et al. can be used to treat disease and the dsRNAs can be delivered via several different means (see column 9, lines 48-64).

37. Thus, Fire et al. disclose all the limitations of claims 1-10, 15-26, 28-30, 62, 63, and 68- 74

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

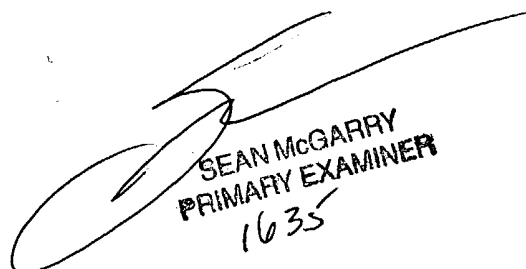
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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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